The promising results of these small early studies prompted a large, multicenter trial, the results of which were recently published. In this study of 241 premature infants, it was found that the administration of 750 U per kg per week of epoetin beta, along with 2 mg of elemental iron per kg per day, significantly reduced the need for transfusions and increased the average hematocrit. Weight gain was decreased in the experimental group, but a high-caloric diet was not used in this study. No adverse effects of epoetin beta were observed, except for a slightly higher incidence of infection. Two possibilities seem most likely to contribute to the higher incidence of infection: the administration of epoetin beta required multiple subcutaneous injections, two of the infants showing induration at the administration site; and treatment with epoetin beta causes an increased use of meager iron stores, which may increase susceptibility to infection. Although this trend in the study was not statistically significant, the observation signifies the need for caution in adopting this therapeutic approach. In other small studies in which infants received 3 to 6 mg of supplemental elemental iron per kg per day, no increased incidence of infection occurred.

Although the increased safety of blood transfusions through the use of single donors and improved viral screening techniques has reduced the risk of transfusion therapy, epoetin is emerging as a possible alternative in the treatment of the anemia of prematurity. Cost analysis has shown little difference between the two approaches. Transfusion therapy costs an average of $1,203 per infant and epoetin beta an average of $1,262. More studies are needed to establish optimal dosing regimens, iron supplementation, and nutritional support for patients receiving epoetin for the anemia of prematurity and to identify which patients are most likely to benefit. Further studies, however, may validate the use of epoetin to prevent or treat the anemia of prematurity.

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Inhaled Nitric Oxide for the Treatment of Persistent Pulmonary Hypertension

PERSISTENT PULMONARY HYPERTENSION is the most important cause of cardiorespiratory failure and the most common indication for treatment with extracorporeal membrane oxygenation (ECMO) in near-term neonates. In persistent pulmonary hypertension, the resistance to the flow of blood through the lungs is high. This results in hypoxemia caused by large right-to-left shunts through the patent ductus and the foramen ovale. Persistent pulmonary hypertension occurs as a primary condition of neonatal maladaptation or as a secondary condition to other diseases such as hyaline membrane disease, meconium aspiration, infection, and congenital diaphragmatic hernia. That most babies with this disorder also have severe parenchymal lung disease complicates their treatment and requires that therapy be aimed at both components. Babies with persistent pulmonary hypertension may also have varying degrees of perinatal hypoxic ischemic encephalopathy.

Nitric oxide is a recently discovered biologic messenger with many physiologic roles. It dilates blood vessels, allows macrophages to kill bacteria, fungi, and tumor cells, and is a neurotransmitter involved in central nervous system functions such as long-term memory. Nitric oxide is thought to be the final regulator of vascular muscle tone at a cellular level. It plays key roles in the regulation of cerebral and coronary blood flow and in overall vascular homeostasis. In humans, the presence of an endogenous inhibitor of nitric oxide synthesis has been suggested as a mechanism for the hypertension of chronic renal failure. Administered inhibitors of nitric oxide synthesis may have a beneficial effect on the hypotension of septic shock. Nitroso-containing compounds, such as nitroprusside, are thought to act through liberating nitric oxide in tissue.

The therapeutic value of inhaled nitric oxide is being studied in other conditions in which pulmonary hypertension plays a role and beyond the neonatal age group. These conditions include surgical and postoperative management of congenital heart disease, the adult respiratory distress syndrome, and idiopathic pulmonary hypertension.

To date, there is no clinically evaluated, selective pulmonary vasodilator that is free of systemic side effects. Studies using inhaled nitric oxide in animals have shown a reversal of pulmonary vasoconstriction, with no apparent effect on the systemic vascular resistance. In neonates and animals with persistent pulmonary hypertension, inhaled nitric oxide used in concentrations of 20 to 80 parts per million has been reported to rapidly improve preductal oxygen saturation. No studies, however, have shown whether inhaled nitric oxide decreases mortality or the need for ECMO in babies with persistent pulmonary hypertension or if it changes the incidence of chronic lung disease or the duration of a hospital stay.

The bedside set-up for administering inhaled nitric oxide should include primary-grade nitric oxide in nitrogen gas, 800 to 2,000 ppm, certified to contain no greater than 8 ppm of nitrogen dioxide and an electrochemical or chemiluminescence analyzer capable of measuring nitric oxide and nitrogen dioxide levels in parts per million. Currently available analyzers may give erroneous values of nitrogen dioxide in the presence of a high fraction of inspired oxygen or may not readily fit in a ventilator circuit. Other hardware includes single-stage diffusion-free regulators, an appropriate flowmeter, and a scavenging system.

Once it reaches the pulmonary circulation through the lung, inhaled nitric oxide almost instantly binds to

reduced hemoglobin, forming nitrosyl-hemoglobin, which is then oxidized to methemoglobin with the production of nitrites and nitrates. Provided methemoglobin levels in the blood remain below 5%, this leads to no clinically important problems. Inhaled nitric oxide does get into platelets and prolongs bleeding time, which has raised the concern that this might lead to an increased risk for neonatal intracranial bleeding. Nitric oxide and its oxidation products (NO_2, NO_x) may also cause direct pulmonary toxicity, particularly to immature lungs. Current occupational safety and health standards consider exposure to 25 ppm for an 8-hour time-weighted average safe. Pulmonary vasodilator concentrations of nitric oxide currently used are in this range, but therapy with nitric oxide will usually involve a 24-hour exposure rather than 8 hours.

Most investigators feel that inhaled nitric oxide is still an experimental therapy, but some centers are currently using inhaled nitric oxide for clinical indications, outside of experimental protocols. Theoretically, any center, large or small, could avail itself of the equipment and know-how to administer inhaled nitric oxide at this stage. Undesirable effects of this might include delayed referral of patients needing level III care and exposure of patients to a possibly toxic gas before its indications, contraindications, and side effects have been fully elucidated by randomized controlled trials in progress.

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Dialysis and Renal Transplantation of Infants

OBSTRUCTIVE UROPATHY, renal dysplasia, and renal cortical necrosis are the most common causes of end-stage renal disease in infants. An interesting occurrence is that asphyxia in the newborn period can damage kidneys out of proportion to brain, leaving an infant with renal cortical necrosis but good potential for intellectual development. Oxalosis and severe congenital nephrotic syndrome are infrequent causes of renal failure.

When infants with severe renal disease fail to grow with conservative management, dialysis may be needed to help an infant grow to a size suitable for transplantation. Dialysis is usually prescribed as a vigorous peritoneal dialysis program, with the infant receiving 12 or more exchanges a day. Besides this dialysis prescription, adequate nutrition must be provided. Infants with renal failure generally have poor appetites, and 90% of them need nasogastric tube feeding or gastrostomy feeding. Daily energy intakes of as much as 140 kcal per kg of body weight may be needed. With such a dialysis and nutrition program, however, growth and development can be well supported and transplantation undertaken if the renal disease does not resolve.

Kidney transplantation is the therapy of choice for infants and children with end-stage renal disease. Transplantation has been accomplished in infants as small as 4.5 kg (10 lb), but is more easily done, with less risk, once the infant has reached 8 to 10 kg (18 to 22 lb). At this size, when the transplantation is done at a center with both a surgeon and nephrologist experienced in caring for infants, the results approach those attained in larger children. Patient survival rates are above 95% at one year and graft survival above 90%. Most donors (70%) used for infants and small children are living-related, usually a parent. Best results are obtained with the use of living donors. Cadaver donors younger than 6 years are not suitable because of rates of graft thrombosis and technical complications.

The kidney is placed in the peritoneal cavity, with anastomoses of the renal artery and vein end-to-side to the aorta and inferior vena cava. The kidney most often lies on the right side, and the right native kidney may be removed to make room. Both native kidneys are removed only if they are thought to be a risk for infection or the cause of severe hypertension. In the immediate postoperative period, urine output is high, but the adult kidney accommodates to the infant's physiology within days.

Infants and small children usually grow and develop well after transplantation. Most are maintained on triple immunosuppressive therapy consisting of azathioprine, cyclosporine, and low-dose prednisone. Tacrolimus (Prograf, called FK 506 during clinical trials before US Food and Drug Administration [FDA] approval) is similar to cyclosporine in action and has recently been approved by the FDA for use in patients with liver transplants. It may also have a role in kidney transplantation, particularly in patients who do not tolerate cyclosporine or who absorb it erratically. Tacrolimus is absorbed rapidly from an empty stomach. New and better immunosuppressive regimens, with better efficacy and fewer side effects than this triple therapy, are on the horizon. If a transplanted kidney does fail, retransplantation is possible.

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Sedation for Pediatric Procedures

THE INCREASE IN the number of diagnostic and therapeutic procedures done on infants and children over the past decade has led to an increased use of sedation for these patients. Imaging studies, bone marrow aspirations, lumbar punctures, dental procedures, cardiac catheterizations, and endoscopies are commonly done with sedation in hospitals and ambulatory clinics. The American Academy of